withdrawal. When they transfected the cells with excess PDE5, they observed increased β-ENaC expression. Additional transfection confirmed that an increase in one of these proteins was matched by increases in the others. The authors do not provide an explanation of how the decrease of cGMP might result in an increase in these proteins, nor why the increase in any one should cause an increase in the others. ENaC is regulated by a complex combination of proteolytic activation, trafficking, ubiquitination, and recycling.[5] None of these seems to account for the increase in abundance in the corin knockout mouse. In addition, it is unclear why only the β-ENaC would be upregulated, given that all three subunits are required for channel activity. It is possible that the decrease in cGMP impacts the degradatory pathway for β-ENaC, although an isoform-specific degradation has not been proposed previously. The observation is intriguing; however, the signaling pathway that could lead to this is still obscure. It might have been interesting to know how both corin and ANP in these cells responded to the withdrawal of cGMP (Figure 1).

PDE5 is present in proximal tubules and collecting duct.[6] Elevated levels of PDE5 have been reported to contribute to renal resistance to the actions of ANP, resulting in Na^+ retention and volume expansion,[3] so elevated levels of PDE5 are not surprising in the nephrotic syndrome animals. What causes the increase is not explained in the article by Polzin *et al.*[1] If corin is decreased, and ANP levels are correspondingly decreased, then the increased PDE5 would not be a response designed to cope with the actions of ANP. PDE5 is cGMP dependent, being phosphorylated to its active form by PKG, and feeds back to degrade the cGMP in a control loop. It seems paradoxical, therefore, that a decrease in cGMP should lead to an increase in PDE5.

A good study is one that provides solid data, presents intriguing theories, and leaves readers with some questions for which they eagerly await answers. This study does all that, and we are left with questions such as: Since corin is a protease, does PDE5 influence the signaling pathway that leads to corin activation? Are there substrates for corin in the kidney other than ANP? Is there any evidence for direct interaction between ENaC and corin? What is the proteolytic enzyme that cleaves β-ENaC in the nephrotic kidney? Why does the decrease in cGMP result in increased levels of these proteins? What is the connection between PDE5 and β-ENaC; are they functionally linked or just coincidentally increased in the nephrotic kidney?

The authors conclude that their findings 'strongly suggest that corin has a key function in the control of Na^+ and water absorption in proteinuric kidney diseases.'[1] By placing corin in the kidney and showing that corin, ANP, and cGMP are reduced in the nephrotic kidney concomitant with increases in β-ENaC, PDE5, pPDE5, and PKGII, Polzin and colleagues[1] provide strong evidence in support of that conclusion.

DISCLOSURE
The author declared no competing interests.

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Kidney transplantation from older donors: proceed with caution

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Kidney transplantation from living and deceased donors above age 60 increased in recent years in response to organ shortage. With careful screening, short-term follow-up of living elderly donors demonstrated stable remaining kidney function even in those with mild and controlled hypertension. The need for confirmation of long-term safety is heightened by the report by Tan *et al.* of a high prevalence of nephrosclerotic changes in these donors and evidence for a decreased number of glomeruli in elderly deceased donors.

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Increased incidence of end-stage renal disease with persistent high morbidity and mortality of dialysis treatment has led to a widening gap between potential recipients and the limited number of organ donors. Older donors, living and deceased, became the resource to fill this need over the past decade (Figure 1). Since 1999, the United Network for Organ Sharing (UNOS) reported an increase in kidney donors above age 65 of 339% and 262% for living and deceased donors, respectively. Initial single-center reports of up to 5-year patient and graft survival of recipients of kidneys from living donors 50–71 years

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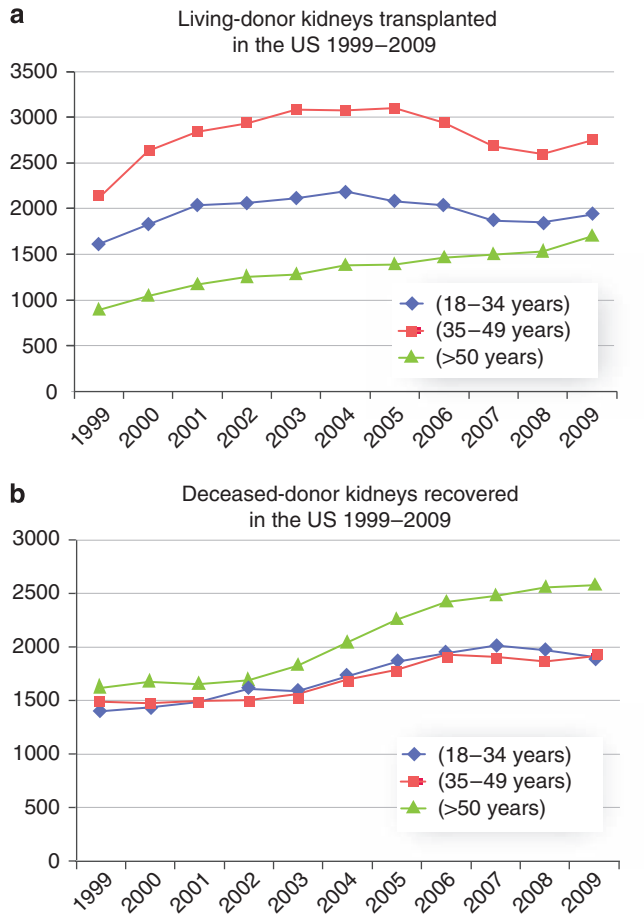

Figure 1 | Trends in the age of living (a) and deceased kidney donors (b) in the United States, 1999–2009. (Based on data from UNOS. http://www.unos.org.)

old are encouraging.[1,2] Patient survival and graft survival were comparable to those of recipients of younger living-donor kidneys, and glomerular filtration rate (GFR) appeared stable, though at a lower level. These short-term outcomes were later confirmed by analysis of the UNOS database, but only for recipients of kidneys from living donors younger than 65 years. Kidneys from donors older than 65 were associated with an up to 70% increase in relative risk of graft loss.[3] The long-term effect of kidney donation on the kidney function of elderly donors has not been reported, but short-term safety[4,5] and extrapolation from the safety of kidney donation in younger donors have encouraged further expansion of the living-donor pool by accepting older donors even with hypertension or minor medical problems.[6]

Tan *et al.*[7] (this issue) now report their study on the effect of aging on remaining kidney function after kidney donation in living donors older than 55 years. Measurements of GFR, blood flow, and cortical volume in the remaining kidney 6 months after donation showed no difference between young and older donors, a finding that should give the community some encouragement. The authors' elegant studies of the glomerular ultrastructure, the single-nephron ultrafiltration coefficient, and histologic evidence of percentage global sclerosis and interstitial fibrosis could not explain the disparity in GFR measurement in a subset of older compared with younger donors. However, in a small subset of older patients with a lower GFR not entirely explained by evident glomerulosclerosis on histologic examination, and on the basis of calculated glomerular number derived from modeled single-nephron GFR and K_f values based on the loss of cortical volume, they caution that the number of functioning glomeruli in these kidneys may reach a threshold value suggesting enough glomerulopenia that progressive glomerulosclerosis due to hyperfiltration may ensue. A recent study by the same group on the functioning of kidneys from deceased elderly donors aged 55–72 years similarly demonstrated a markedly decreased number of functioning glomeruli in those kidneys compared with those from donors aged 18–32.[8]

Evidence from the new report by Tan *et al.*[7] and from the recent study by Rule *et al.*[9] calls for more caution in accepting kidney donors above the age of 60. In this group of carefully screened donors, histologic evidence of nephrosclerosis was present in more than 50%.[9] Together the two studies raise several important questions. First, what are the long-term effects on the function of the remaining kidney in the elderly donors? Second, what is the overall outcome of graft and patient survival when kidneys from elderly living donors are transplanted in young recipients? Third, what is a practical and reliable measure of the number of functioning glomeruli when living donors above age 50 are evaluated?

To help answer these important and controversial questions, Tan *et al.* will need to validate their conclusions with further reports on the reproducibility and hopefully a more practical measure of the number of functioning glomeruli. Also, a report on the follow-up of the subgroup of elderly donors with significantly decreased numbers of functioning glomeruli will lend further credence to their mathematical assumptions. As earlier cohorts of elderly living donors with good short-term outcome should have more than 10 years of follow-up,[4,5,10] reporting of long-term outcomes in these donors would provide the community with very clear guidance. Until then, the transplantation community should proceed to use donors above age 60, but with caution.

DISCLOSURE
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